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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,002	KOLTERMANN ET AL.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *7-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on January 11, 2007 has been entered. The claims pending in this application are claims 1-18. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on January 11, 2007.

Election/Restrictions

2. This application contains claims 9-15 drawn to an invention nonelected with traverse in the response filed on May 30, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments

In page 11, second paragraph of applicant's remarks, applicant argues that "[R]egarding the restriction requirement, Applicants note that the Examiner has made the requirement final. Nevertheless, the basis for the restriction requirement remains unclear. According to the Examiner, 'as shown in previous office action, the restriction is based on that different and distinct searches will have to be performed for Groups I and II.' However, Groups I and II were both identified as being searched in class 435, subclass 6. Applicants concede that the Examiner also alleged that the search of Group I would not require a search for step (c) of claim 10, and that of Group II would not require a search for step (c) of claim 18. However, Applicants do not understand how this fact, which would be true of any dependent claim, makes, for example,

claims 1 and 9 independent and distinct. Rather, the claims all appear to involve closely related subject matter and should be examined together in this one patent application. Therefore, even though the Examiner has made the restriction requirement final, Applicants respectfully request that the Examiner reconsider and withdraw it".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the restriction requirement so that Groups I and II will be examined together. First, although Groups I and II are both identified as being searched in class 435, subclass 6, the restriction is not based on classifications of Groups I and II as argued by applicant. Furthermore, the restriction is not based on "the claims all appear to involve closely related subject matter and should be examined together in this one patent application" as argued by applicant. Second, as shown in the office action mailed on March 31, 2006, the restriction is based on that different and distinct searches will have to be performed for Groups I and II. For example, the search required for Group I such as step (c) of claim 18 is not required for Group II while the search required for Group II such as step (c) of claim 10 is not required for Group I. Third, distinct searches will have to be performed for claim 1 in Group I and claim 9 in Group II. For example, the search required for claim 9 of Group II such as step (c) of claim 9 is not required for claim 1 of Group I.

Claim Objections

3. Claim 5 is objected to because of the following informality: "step (a) to" should be "step (a)".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 5 is rejected as vague and indefinite. Since claim 4 only has one step (a), it is unclear what means the phrase "one or more of step (a)". Please clarify.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-8, 16, and 18 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Patten *et al.*, (US Patent NO. 6,335,160 B1, filed on December 18, 1996).

Regarding claims 1-8 and 16, Patten *et al.*, teach providing at least one polynucleotide having at least one differing site and randomizing the polynucleotides (ie., fragmenting randomly using a type II restriction enzyme such as Sfi I) at or in a proximity to the at least one differing

site as recited in claim 1 wherein the polynucleotide is double-stranded and is derived from at least one starting single-strand polynucleotide or is a heteroduplex generated from at least two polynucleotides that differ in at least one site from each other as recited in claim 2 and the polynucleotides or their corresponding translational products are pre-selected with respect to their genotypic and/or phenotypic features as recited in claim 3, further comprises the following steps : (a) providing polynucleotides that differ at one or more sites from each other, whereby these differing sites define start points for randomization; (b) generating heteroduplices from these polynucleotides; c) recognizing resulting mismatching sites; (d) selectively randomizing the polynucleotide at or in proximity to these mismatching sites as recited in claim 4 wherein one or more of steps (a) to (d) are carried out for multiple cycles before a next step is carried out as recited in claim 5, the at least one differing site of the polynucleotide consists of one or more mutations, and the mutations comprise (i) one or more nucleotide substitution (s), (ii) one or more nucleotide insertion (s), (iii) one or more nucleotide deletions), or (iv) a combination of (i) to (iii) as recited in claim 6, further comprises selection or screening for at least one randomized polynucleotide or its corresponding translational products towards a desired property as recited in claim 7, the method of claim 1 is carried out cyclically (ie., repeating method steps taught by Pattern *et al.,*) as recited in claim 8, and providing variants of the polynucleotide sequence having at least one differing site and randomizing the polynucleotide sequence at or in proximity to the differing sites as recited in claim 16 (see columns 1-7, 10, 11, 17, columns 105-110). Note that, since Patten *et al.,* teach fragmenting DNA randomly using a type II restriction enzyme such as Sfi I (see columns 10, lines 35-53 and column 17, lines 23-50), the cutting site of Sfi I contains random nucleotides (see attachment for Sfi I) and some random nucleotides in the

cutting site of Sfi I are replaced by other nucleotides in later steps, Patten *et al.,* do disclose randomizing polynucleotides at specific sites.

Regarding claim 18, Patten *et al.,* teach (a) introducing stochastically random mutations into polynucleotides to generate a population of polynucleotides; (b) selecting or screening the population of polynucleotides generated in step (a); (c) isolating those polynucleotides which encode gene products with improved characteristics; (d) selectively randomizing the polynucleotides at or in proximity to those site(s), at which the polynucleotide isolated in step (c) differ from each other; e) selecting or screening a population of polynucleotides generated in step (d); (f) isolating those polynucleotides which encode gene products with further improved characteristics, in the above method steps (a) to (c) and/or steps (d) to (f)a and/or steps (a) to (9 are optionally repeated iteratively (see columns 1-7, 10, 11, 17, and columns 105-110). Note that, since Patten *et al.,* teach fragmenting DNA randomly using a type II restriction enzyme such as Sfi I (see columns 10, lines 35-53 and column 17, lines 23-50), the cutting site of Sfi I contains random nucleotides (see attachment for Sfi I) and some random nucleotides in the cutting site of Sfi I are replaced by other nucleotides in later steps, Patten *et al.,* do disclose randomizing polynucleotides at specific sites.

Therefore, Patten *et al.,* teach all limitations recited in claims 1-8, 16, and 18.

Response to Arguments

In page 12, last paragraph bridging to page 15, first paragraph of applicant's remarks, applicant argues that "[P]atten does not teach 'providing at least one polynucleotide having at least one differing site and selectively randomizing the polynucleotides at or in a proximity to the at least one differing site' as required by the rejected claims" because "[A]s stated above, the

present claims are directed to the 'selective randomization' of polypeptides. The term 'randomization' in this context is random substitution of the original nucleotides at selected sites. These selected sites, in turn, are those selected sites at which two or more polynucleotides differ from each other in their nucleotide sequence with any other possible nucleotide. As one original nucleotide is replaced with any other nucleotide without predicting or selecting a specific replacement nucleotide, such replacement is random. As opposed to 'DNA shuffling' methods, this randomization entails the substitution of a variety of mutagenic replacement nucleotides that do not necessarily appear in any of the starting genes at these positions (as stated, the starting genes may have an 'A' and a 'G' at a particular mismatch position, and the claimed invention earl target mutagenesis to create clones with 'A', 'G', 'C' or 'T' at this 'selected' position.) In this and other ways, the claimed invention is, thus, distinct from recombination (shuffling) methods. Moreover, in the claimed invention, no sequence related determination is needed to effect either the selection of these sites or their randomization. In contrast, 'randomizing the polynucleotides,' as described by Patten, involves fragmentation that occurs randomly throughout the gene. The fragmentation does not direct randomization of the substitutions at any positions, let alone targeted or selected positions, and, thus, even if, assuming for the sake of argument, it could be considered 'random,' it is certainly not 'selectively randomizing,' as required by the instant claims. Instead, Patten's fragmentation generates fragments that are later reassembled to mix and match differing gene segments from the starting genes. It is, thus, a method for 'shuffling' the preexisting mutations of the parental genes (see, for example, column 1, lines 45-67, and column 2, lines 25-67, of Patten.) At no point does Patten describe or in any way suggest the randomizing of polynucleotide sequences at sites at which variants differ, but,

rather, the random reassembly of fragments of starting genes that carry only the mutations of the parents. Where Patton does describe 'random mutagenesis,' it is either site directed using primers, and, thus, requires a previous sequence related determination in order to design and synthesize the 'two regions complementary to the DNA' on the oligonucleotides (see, for example, column 3, lines 1-17, of Patten), or is random across the gene and, thus, does not have the component of only randomizing or mutating 'specific sites' (see, for example, column 7, lines 23-35, of Patten.) Also, none of the claims of Patton relate to a method of randomization at specific sites with no sequence related determination needed. For example, claim 16 includes only methods of recombination (shuffling), not randomization at 'specific sites' and the 'segment' that forms the substrates for recombination must be pre-selected using sequence information in order to design and synthesize the described needed nucleotides. Some of Patten's dependent claims 17-36 include mutagenesis, but using oligonucleotides with mutations at pre-selected locations and, thus, requiring sequence information, or using random uracil incorporation and, thus, not targeting specific sites, both of which are key aspects of the instantly claimed invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, applicant's statement "[T]he term 'randomization' in this context is random substitution of the original nucleotides at selected sites" in the arguments is incorrect and the term "randomization" cannot related to selected sites because the specification defines "randomization" as "the manipulation of polynucleotides by unpredicted, stochastical replacements of the original nucleotide at a position with any other nucleotide" (see page 12, last paragraph). Second, although applicant argues that Patten *et al.,* do not teach randomization at

specific sites, this limitation is not in the contents of claims. The recitation "randomizing polynucleotides at specific sites" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Third, since Patten *et al.,* teach fragmenting DNA randomly using a type II restriction enzyme such as Sfi I (see columns 10, lines 35-53 and column 17, lines 23-50), the cutting site of Sfi I contains random nucleotides (see attachment for Sfi I) and some random nucleotides of the cutting site of Sfi I are replaced by other nucleotides in later steps, Patten *et al.,* do disclose providing at least one polynucleotide having at least one differing site and randomizing the polynucleotides (ie., fragmenting randomly using a type II restriction enzyme such as Sfi I) at or in a proximity to the at least one differing site.

9. Claim 17 is rejected under 35 U.S.C. 102(e) as being anticipated by Padgett *et al.,* (US 2002/0177160 A1, priority date: February 2, 2001).

Regarding claim 17, since Padgett *et al.,* teach preparing at least one heteroduplex polynucleotide, combining said heteroduplex polynucleotide with an effective amount of an agent or agents with exonuclease activity, polymerase activity, and strand cleavage activity, allowing sufficient time for the percentage of complementarity between strands of the heteroduplex polynucleotide to increase, wherein diversity in the population is increased, and

screening or selecting a population of variants for the desired functional property (see page 29, claim 51) and the heteroduplex polynucleotide has mismatches (see abstract) wherein the agent with strand cleavage activity is CEL I or T4 endonuclease VII or T7 endonuclease I or SP nuclease (see page 28, claim 16) which is an endonuclease for cutting mismatches (see page 11, [0114]), Padgett *et al.*, disclose randomizing the polynuclcotide sequence only at those sites (ie., mismatch sites) at which these variants differ from each other and selecting or screening a randomized pool of polynucleotides for desired properties.

Therefore, Padgett *et al.*, teach all limitations recited in claim 17.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

March 30, 2007

FRANK LU
PRIMARY EXAMINER